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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,215	10/02/2003	Roland Callens	05129-00072-US	9641

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EXAMINER	
KOSAR, ANDREW D	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/677,215	CALLENS ET AL.	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *8,13-22,29 and 33-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments/Amendments

Applicant's arguments and amendments filed November 13, 2006 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

With regards to the restriction/election requirement, Applicant argues that the election of species is improper and that, "The exact amino acid structure of the peptide is not important as long as A, a peptide chain, comprises at least two enantiopure amino acids." (Remarks, page 11). Applicant further argues that claim 8 should not be withdrawn from consideration.

Respectfully, the examiner disagrees. Claim 8 does not read upon a method of making the elected peptide, GFLG, but rather on making a branched peptide and thus is withdrawn. If claim 1 were to be found allowable, then claim 8 would likely be rejoined. With regards to the election of species, the requirement is proper, as Applicant has clearly drawn method claims to using a single tripeptide, e.g. claim 12, and the search for the method of making one peptide would not necessarily lead to the discovery of making another, as each requires a separate search of the starting material which are structurally different, as a search of the tripeptide FLG as a starting material would not necessarily lead to the discovery of the hexapeptide RGLMNR being used in the methods. Furthermore, Applicant has not clearly stated on the record that the method of making one peptide would be obvious over another peptide. The requirement is deemed proper and made final.

Claims 1-36 and new claims 37 and 38 are pending.

Claims 8, 13-22, 29 and 33-36 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 13, 2006.

Claims 1-7, 9-12, 23-28, 30-32, 37 and 38 have been examined on the merits.

Claim 9 remains objected to because of the following informalities, for the reasons of record and those set forth below:

Claims 9 recites, "a fragment C", which would more clearly recite via usage of another identifier, e.g. Q, Z, X', etc., as C is generally reserved for use in identifying carbon.

Applicant argues that it is not confusing (Remarks, page 13). The examiner respectfully disagrees, as the formula (VI) in claim 9 recites C twice (as a methylene unit and a carbonyl), and could generate confusion in reading the claim. Appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9-12, 23-28, 30-32, 37 and 38 remain rejected/are under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons of record and those set forth below.

Claim 1 is unclear and indefinite as it recites, "Y is chosen from H and cations", however Y is attached as COOY which does not designate any charge in the claims, and thus it is unclear whether Y is a cation before binding to carboxylic acid, or whether it is a cation that forms a salt of the carboxylic acid, i.e.- COO^-Y^+. For example, *t*-butyl cation is used in forming a carboxylic acid ester. Applicant has not addressed this grounds of rejection specifically, and thus the

rejection is maintained.

Claim 1 recites, "R^1 ad R^2 together form a cycloalkyl", however it is unclear how they can form anything other than a heterocycle, as they are attached to a nitrogen and would necessarily require that it be part of any cyclic structure formed, and thus the claims are indefinite. Applicant has not addressed this grounds of rejection specifically, and thus the rejection is maintained.

Claim 1 recites, "HN-A-COOH" and "HN-A-COOY" for formulae (I) and (II) where A 'denotes a peptide chain', however in view of the specification, it is unclear whether the recitation "HN-A-COOH" is defining a peptide as a unit $(NH\text{-}CHR\text{-}CO)_{n\geq 2}$, or whether A alone is a peptide chain attached to an NH and a COOH at the termini, i.e. NH-$(NH\text{-}CHR\text{-}CO)_{n\geq 2}$-COO or NH-$(CO\text{-}CHR\text{-}NH)_{n\geq 2}$-COO, and thus the claims are indefinite.

Additionally, Claims 9 recites, "HN-B" in formula (VI) and B 'is an amino acid or a peptide', however, it is unclear whether the HN moiety is from B, i.e. the N-terminus of the amino acid/peptide, or separately attached to the N-terminus i.e. NH-(NH-CHR-CO) or NH-(CO-CHR-NH), and thus the claims are indefinite.

With regards to claim 1 and 9, Applicant argues that it is clear from the specification that the NH and COO define the N- and C- termini (Remarks,, page 15). Respectfully, the examiner disagrees. First, B does not have a C-terminus presented and second, only the final C-terminal amino acid would have a COO group. One would not clearly understand that A or B is not NH-$(NH\text{-}CHR\text{-}CO)_{n\geq 2}$-COO or NH-$(CO\text{-}CHR\text{-}NH)_{n\geq 2}$-COO, particularly when dependent claims recite that A is FLG tripeptide, rather than reciting that NH-A-COOY is FLG tripeptide.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

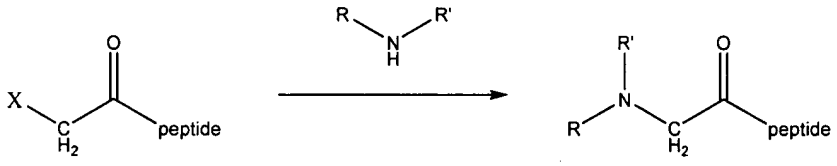
Applicant argues first against each reference separately: that Smales does not teach the synthesis, Saha produce peptoids which have no chiral centers, Marinzi uses a resin/support and Mimura does not teach synthesis of longer peptides. Applicant argues that the instant method is in solution, not on a support, and that there is no disclosure or suggestion in the combined teachings to practice the method as claimed. Applicant further argues that Anteunis does not render obvious the invention in combination with the other references or rectify their alleged defects.

Respectfully, the examiner disagrees. Y is indefinite above, and reasonably interpreted, can be considered to be a resin (when Y is a cation). Furthermore, the art clearly recognizes the method of coupling two amino acids into a dipeptide using the same reaction mechanism as instantly claimed. The art further shows the application of the reaction where the C-terminus is attached to a resin or where a peptoid is used in place of a peptide. On, or off, a resin, the reaction occurs only at an N-haloacyl group, and does not occur at the carboxylic acid terminus or at any free, unprotected side chain residue or any alkyl side chain. Hence, the absence of protecting groups in Marinzi. It is clear the reaction is well understood to occur only at a

haloacyl moiety, and thus the wide use in varied synthetic applications. Thus, contrary to Applicant's assertion, it would have been obvious to have combined the references to arrive at the instantly claimed synthesis, particularly in view of the teachings that provide motivation that each of the identified methods teach specific benefits that are derived, i.e., improvements/enhancements to that which is already well known in the art. Furthermore, Applicant has provided no evidence of an unexpected result being achieved in practicing the method as claimed.

Claims 1-7, 12, 23-28, 30-32, 37 and 38 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over SMALES (PTO-1449, 10/02/03) in view of MARINZI (C. Marinzi, et al. Bioorg. Med. Chem. (2001) 9, pages 2323-2328), SAHA (U.K. Saha and R. Roy. Tetrahedron Letters (1995) 36(21), pages 3635-3638) and MIMURA (US Patent 6,197,998 B1).

The instant claims are drawn to a method of making compounds via the general reaction scheme:



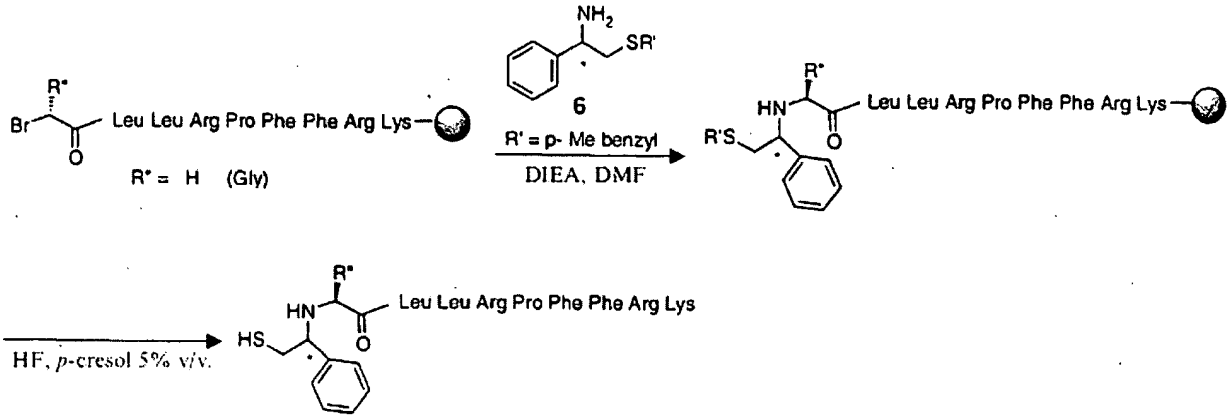
, where X is Br or Cl, where the product is the tetrapeptide GFLG and the amine is ammonia.

Smales teaches the peptide GFLG (e.g. Scheme Page 1558).

The difference between Smales and the instant claims is that while Smales teaches the product, Smales does not teach the synthesis as instantly claimed.

The art recognizes reactions of various amines with haloacetylated amino acids, peptides and peptoides to generate N-Gly-peptides (e.g. Canne and Amatsu (EP 0687501A1) which are cited to show the state of the art).

Marinzi teaches synthesis of N^{α}-substituted Gly-Peptide using bromoacetylated peptides:



(page 2324, Scheme 1) and further teaches that the method is an "easy and quantitative route for the derivatization of the peptide" (page 2325).

Saha teaches synthesis of peptoids, N-substituted polyglycine peptides, using bromoacetylated submonomers in the reaction (e.g. Scheme 2, page 3636). The synthesis is conducted without a resin (solution phase).

Mimura teaches synthesis of chloroacetyltyrosine (Example 1, column 4) and synthesis of GlyTyr via reaction of chloroacetyltyrosine with 28% aqueous ammonia (Example 2, column 5). Mimura teaches that the synthesis of this dipeptide via this mechanism is favored because the product can be formed in "one step in high yields." (column 3, lines 52-53).

It would have been obvious to have made the peptide of Smales, or any other peptide, via reaction of the haloacetylated fragment with ammonia or any substituted amine, on a resin or in solution phase, in order to form the final product more efficiently with fewer steps and higher yields.

One would have been motivated to have made any peptide, including the peptide GFLG, from the haloacetylated form, on a resin or in solution phase, in order to have an easy and quantitative route for derivitizing peptides and to reduce the number of steps in the process, such

as protection/deprotection steps, increase the efficiency of the production and the yield of the product.

One would have had a reasonable expectation for success in forming the product via reaction of the haloacetylated tripeptide with ammonia, as the art recognizes that the reaction of ammonia with haloacetylated amino acids and the reaction of amines with haloacetylated peptides of any size, both on a resin and in solution phase.

Further, with regards to the temperature and concentration ranges, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g.temperature ranges, concentration of reactants), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05). One would have been motivated to optimize the conditions in order to achieve the most efficient reaction possible, with a reasonable expectation for success, as they are art recognized variables that are routinely determined and optimized.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Please note, the limitations of claims 9 and 10 are met in that the claimed method steps

comprise reacting 'a fragment of formula (V)' with C. The broadest reasonable interpretation includes, but is not limited to, reaction of one amino acid with a dipeptide followed by a reaction to generate the haloacetyl moiety, as 'comprising' does not preclude the presence of other steps, and additionally, the broadest reasonable interpretation of 'a fragment of' includes, e.g. B alone.

Claims 1-7, 9-12, 23-28, 30-32, 37 and 38 reamin/are rejected under 35 U.S.C. 103(a) as being unpatentable over SMALES (PTO-1449, 10/02/03) in view of MARINZI, SAHA and MIMURA, as applied to claims 1-7, 9, 10, 12, 23-28 and 30-32, *supra*, and in further view of ANTEUNIS (US Patent 4,725,645; PTO-1449, 10/02/03).

The instant claims are presented *supra*, and are further drawn to the method where the reactant forming products of formula (II) are activated with persilylation.

The teachings of Smales, Marinzi, Saha and Mimura are presented *supra*.

Anteunis teaches using silated amino acids during peptide synthesis, "makes it possible to carry out a rapid coupling reaction in continuous fashion, which reaction takes place without racemisation and can be carried out in the absence of basic coreagents, with water optionally present and in the presence of known protecting agents. In addition, it enables peptides of high molecular weight to be produced in yields higher than those obtained with the known silylating agents. Moreover, the process of the invention enables the water to be chemically consumed and volatile silyl derivatives to be obtained, which facilitates the removal of the later (column 1, line 60 to column 2, line 3).

It would have been obvious to have used silyl activated peptides or amino acids to form the building blocks in order achieve rapid coupling reactions between the subunits.

One would have been motivated to silyl activate the peptides in order to increase the

speed and efficiency of the reaction and reduce racemization of the product.

One would have had a reasonable expectation for success in forming the starting material by reaction of silyl activated peptides, as silyl activation and the subsequent use in the synthesis of peptides is a widely practiced technique that can be used to make any peptide.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 8, 13-22, 29 and 33-36 drawn to an invention nonelected with traverse on May 31, 2006 and again in the response of November 13, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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